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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,633	06/08/2001	Preeti G. Lal	PC-0040 CIP	9282

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,633	LAL ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,28-31 and 33-42* is/are pending in the application.

4a) Of the above claim(s) *35-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26, 28-31, 33, 34 and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed February 12, 2004 amending the specification to remove active hyperlinks and correct references to the sequences on pages 9-10, canceling claims 24, 25, 27 and 32, amending claims 26, 28, 29, 31, 33, 34 and adding claims 40-42 has been entered.

The Declaration under 37 CFR § 1.132 by Dr. John Rockett filed February 12, 2004 has been entered.

The Declaration under 37 CFR § 1.132 by Dr. Vishwanath Iyer filed February 12, 2004 has been entered.

Claims 26, 28-31 and 33-42 are pending. Claims 35-39 are withdrawn. Claims 26, 28-31, 33, 34 and 40-42 are under consideration.

Specification

The disclosure is objected to because as amended February 12, 2004 it refers to the percent identity between SEQ ID NO:2 and a clone (specification at pages 9-10). The alignment makes sense only between two sequences. Without knowing the sequence of the clone, it is impossible to make an alignment between the sequence of the clone and SEQ ID NO:2. The deletion of the row, for example, is suggested.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 40 is drawn to a polynucleotide encoding an immunogenic portion of a polypeptide consisting of an amino acid sequence of SEQ ID NO:1, said portion consisting of at least 5 contiguous amino acid residues of SEQ ID NO:1.

Applicants indicate support for new claims 40-42 "at page 2, lines 15-25 and page 7, lines 4-5" (Remarks, page 8). Careful reading of the indicated texts The Examiner is unable to locate adequate support I the indicated texts. The specification at page 2, lines 15-25 supports a specific fragment of SEQ ID NO:2 selected from the group consisting of SEQ ID NOs: 3-8 and provides no support for any fragment of SEQ ID NO:2 encoding at least 5 amino acids. Moreover, it does not support a DNA, i.e. degenerate variants of SEQ ID NO:2 encoding the same. At page 7, lines 4-5, the specification provides a definition of an oligopeptide as "an amino acid sequence from about five residues to about 15 residues that used as part of a fusion protein to produce an antibody". The specification is silent with regard to a polynucleotide encoding said oligopeptide. Thus there is no indication that a polynucleotide encoding an

immunogenic portion of a polypeptide consisting of an amino acid sequence of SEQ ID NO:1, said portion consisting of at least 5 contiguous amino acid residues of SEQ ID NO:1 was within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 26, 28-31, 33, 34 and 40-42 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 26, 28-31, 33, 34 and 40-42 are directed to or depend from a DNA encoding SEQ ID NO:1. Applicants disclose a human nucleic acid sequence of SEQ ID NO: 2 encoding the protein having the amino acid sequence of SEQ ID NO:1. The asserted utility for SEQ ID NO:2 is as diagnostic of cancers, particularly lymphoma and cancer of the bladder, colon, kidney, ovary, and testis (page 3, lines 4-5). The specification teaches that SEQ ID NO:1 has 55% identity to both high-glucose-regulated protein 8 and NY-REN-2 antigen (page 8, lines 32-33). There is no additional data to support any function for the protein of SEQ ID NO:1. Neither high-glucose-regulated protein 8 nor NY-REN-2 antigen are used as diagnostic of cancer. The specification

discloses the expression of SEQ ID NO:2 in various libraries, each library constructed from the tissue removed from a single individual. With regard to lymphoma (one library), expression was two-fold greater than in activated lymphocytes and six-fold greater than in untreated or non-activated T-cells (page 32). The specification teaches that "no expression was seen in activated in three other libraries made from activated T-cells (page 32, line 31). With regard to cancer of the colon, the specification teaches that in metastatic cancer (one library) the expression was higher than in contained tumor (one library) and two-fold greater than in normal tissue (page 32, line 33, through page 33, line 18). With regard to cancer of the bladder, the expression is higher in one library in transitional cell carcinoma of the bladder (BADTUT08) than in normal tissue (page 33). With regard to cancer of the kidney, the expression is higher in one library in Wilms' tumor, slightly higher in one library in renal cell carcinoma and less high in two other libraries in renal cell carcinoma compared with one library from normal cortex. With regard to the ovary, only in one metastatic endometrial cancer library and not in other cancerous and non-cancerous ovarian libraries the expression was greater (page 34). With regard to the testis, one library from testis tumor has higher expression than one library from embryonal carcinoma, the latter one higher than in normal tissue. Thus, it appears, that the specification presents data mostly obtained from one individual (one library) and compares it to library/libraries from other individuals. Unless the data are statistically significant, it is impossible to know whether the expression is indeed diagnostic of any cancer. It is known in the art that the expression of a protein can vary from one individual to another. On the other hand, in the state of cancer, the expression

of most proteins is aberrant. Therefore, the specification provides no guidance as to how to correlate the expression of SEQ ID NO:2 and the specific cancer. Said correlation is not established in the prior art.

While the expression of SEQ ID NO:2 is may be indicative of cancer, it may be due to other conditions as well. The expression of a gene can be affected by various conditions not necessarily associated with or occurring in any type of cancer. Overall, SEQ ID NO:2 appears to be expressed or not expressed in cancerous as well as non-cancerous tissues (*supra*, and page 34, lines 38-40, for example).

Thus, there is no showing in the specification that the expression of SEQ ID NO:2 is specifically occurring in lymphoma and cancer of the bladder, colon, kidney, ovary, and testis and not other diseases or in healthy condition. Alternatively, there is no showing that the expression of SEQ ID NO:2 parallels the expression of any gene used as a direct diagnostic tool for any type of cancer.

However, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells of one individual is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule in a statistically significant manner. There must be some expression pattern that would allow

the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself.

Thus, obtaining of theoretically desired result of diagnosing lymphoma and cancer of the bladder, colon, kidney, ovary, and testis by measuring the expression of SEQ ID NO:2 is unpredictable based on the instant disclosure. A method for diagnosing of lymphoma and cancer of the bladder, colon, kidney, ovary, and testis would require or constitute carrying out further research to identify or reasonably confirm that cancer can be diagnosed using a DNA encoding SEQ ID NO:1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28-31, 33, 34 and 40-42 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 34 is rejected under 35 U.S.C. 102(a) as being anticipated by Hillier et al.

Hillier et al. (GenBank EST, accession AA398704, August 12, 1997) the 447 bp human EST. The nucleotides 1-274 of said EST are 100% identical to nucleotides 1755-2028 of SEQ ID NO:2.

Claim 34 has been amended to recite a polynucleotide consisting of at least 60 contiguous nucleotides of a polynucleotide of claim 33. Because a polynucleotide of claim 33 is a polynucleotide comprising SEQ ID NO:2 not consisting of SEQ ID NO:2, the EST of Hillier et al. anticipates claim 34.

Response to Arguments

Applicant's arguments filed February 12, 2004 have been fully considered but they are not persuasive.

Applicants argue that "The instant application is a continuation-in-part application of and claims priority to United States patent application Serial No. 08/933,750 "the Lal '750 application") filed on September 23, 1997. The SEQ ID NO: I-encoding polynucleotides were described in the Lal '750 application" (Remarks, paragraph bridging pages 10-11). The examiner agrees with that.

Applicants continue to state "the First Bedilion Declaration, Rockett Declaration, Iyer Declaration, Second Bedilion Declaration, and the ten (10) references fully establish that, prior to the September 23, 1997 filing date of the parent Tang '808 application, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types call be used as hybridization probes - that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;
>
> with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;
>
> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible',

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene

to the microarrays they sell;

it is not necessary that the biological function of a gene be

known for measurement of its expression to be useful in drug discovery and

lead optimization analyses, toxicology, or molecular phenotyping experiments;

failure of a probe to detect changes in expression of its cognate

gene does not diminish the usefulness of the probe as a research tool; and

failure of a probe completely to detect its cognate transcript in

any single expression analysis experiment does not deprive the probe of

usefulness to the community of users who would use it as a research tool.

As demonstrated by the First Bedilion Declaration, the Rockett Declaration, the Iyer Declaration, and the Second Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise biological function.

In his Declaration, Dr. Rockett explains the many reasons why a person skilled in the art in 1998 would have understood that any expressed polynucleotide is useful for a number of gene expression monitoring applications, *e.g.*, in cDNA microarrays, in connection with the development of drugs and the monitoring of the activity of such drugs" (pages 11-12, emphasis added).

The examiner notes that first, no Second Bedilion Declaration has been filed in the instant application; second, '808 Tang application is not related to the

instant application and third, the publications filed with the Declarations and Remarks have never been mentioned in the specification or supplied with IDS.

The First Bedilion Declaration has been discussed in detail in the last Office action mailed November 10, 2003 (pages 13-21).

The Rockett Declaration and the Iyer Declaration filed February 12, 2004 and the Remarks by Applicants argue the general use of any expressed DNA. None of these documents discloses or provides any information specifically about a DNA encoding SEQ ID NO:1, including SEQ ID NO:2.

The examiner notes that the specification lacks any mentioning of toxicology testing. While toxicology testing may be known in the art at the time of filing, as an essential element, it should be described in the specification.

The examiner does not argue the utility of cDNA microarrays in general that is supported by the above Declarations and literature. The importance of toxicology testing and the use of DNA arrays therefor is unquestionable. What is not agreed with is the usefulness of a microarray comprising a DNA encoding SEQ ID NO:1 if the same microarray without it did not have utility. Furthermore, the specification does not disclose what drug(s) SEQ ID NO:1 would be useful in developing, or what disease(s) it would be useful in diagnosing. As explained in the rejection above, the specification provides no basis for concluding that SEQ ID NO:1 is associated with any specific disease.

With regard to the specific utility of a DNA encoding SEQ ID NO:1 including SEQ ID NO:2, Applicants argue that "Appellants' submission of additional facts overcomes

this concern [rejection]. Those facts demonstrate that, far from applying ***regardless*** of the specific properties of the claimed invention, the utility of Appellants' claimed polynucleotides as gene-specific probes ***depends*** upon specific properties of the polynucleotides, that is, their nucleic acid sequences" (page 23, emphasis added). Applicants recite the Rockett and Iyer Declarations to assert that "[E]ach probe on . . . [a "high density spotted microarray[]"], with careful design and sufficient length, and with sufficiently stringent hybridization and wash conditions, ***binds specifically*** and with minimal cross-hybridization, to the probe' s cognate transcript"; "[[e]ach gene included as a probe on a microarray provides ***a signal that is specific to the cognate transcript***, at least to a first approximation." Accordingly, "each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of this analytical device for gene expression profiling" ; equally, "[e]ach new gene-specific probe added to a microarray thus increases the number of genes detectable by the device increasing the resolving power of the device" (page 23).

Applicants continue "Although not required for present purposes, it would be appropriate to state on the record here that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of many, perhaps most, molecular biological techniques developed over the past 30- 40 years.

For at least the above reasons, withdrawal of the rejection under 35 U.S.C. 101 is respectfully requested" (paragraphs bridging pages 23-24).

In conclusion, it would appear that Appellants are using the asserted microarray utility to provide a utility that can be asserted for any isolated cDNA, regardless of how little is known about it, which (they hope) will nonetheless serve as a basis for patent protection of all related products and methods and secure for Appellants any value that might become apparent in the future, after they or others have further characterized the claimed products. It was precisely this type of result that the Brenner Court sought to avoid by requiring disclosure of a substantial utility to satisfy § 101. See 148 U.S. at 535-36, 148 USPQ at 696: [The Court was not] "blind to the prospect that what now seems without 'use' may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Id.

The polynucleotides of the instant claims may indeed prove to be very useful (and valuable), after the in vivo role of the encoded protein is discovered. The work required to confer value on a polynucleotide encoding SEQ ID NO:1, however, remains to be done.

Finally, it is noteworthy that no claims on appeal is directed to the microarray on which Appellants base most of their broad assertions of utility. In addition to a polynucleotide encoding SEQ ID NO:1, Appellants also claim a recombinant polynucleotide containing a polynucleotide encoding SEQ ID NO:1 and a vector, a host cell containing thereof and a method of making the protein of SEQ ID NO:1. Neither the

method nor either product has any apparent use in a microarray gene-expression assay.

The rejections not discussed above are withdrawn in view of the amendment.

Conclusion

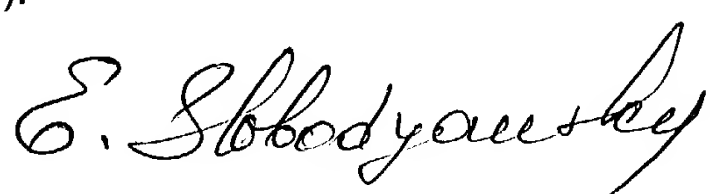
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

April 29, 2004